The pathogenesis of oedema in kwashiorkor—the role of plasma proteins

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The concept that hypoproteinaemia is significant in the development of oedema in kwashiorkor is superficially a simple one. Starling (1896) described the physical forces operating between the intravascular and extravascular compartments and from his work it is evident that when plasma protein concentration decreases a reduced plasma colloid osmotic pressure would be expected to produce decreased oncotic differences between plasma and interstitial fluid that would lead to increased filtration, decreased venous absorption and oedema; but inadequacies in this view have been apparent for some time. For example, oedema does not form continuously as plasma protein concentration decreases, in fact our own experience would suggest a threshold for oedema formation at an albumin concentration of 20–25 g/l, and when it does occur the extent of oedema in individual children does not correlate particularly well with plasma protein concentration. The failure to explain these broadly clinical observations has generally led workers to abandon the idea that changes in plasma colloid osmotic pressure are of major significance and to turn to other explanations, notably those centred around the retention of sodium and water (Klahr & Alleyne, 1973).

It is, however, intended that this paper should provide a reappraisal of the case for hypoproteinaemia as a factor of significance in oedema pathogenesis. To do this it will be necessary to consider first the relationships between plasma protein concentration and colloid osmotic pressure.

Plasma colloid osmotic pressure and protein concentration

By virtue of its relatively low molecular weight albumin exerts a greater oncotic effect than many other plasma proteins and this is acknowledged in a number of empirical or theoretical formulas devised for the prediction of colloid osmotic pressure from protein concentration (see Coward, 1975). Formulas of this type all indicate that the oncotic effects of equivalent changes in protein concentration are larger when protein concentrations are high than when they are low; thus it might be surmized that the oncotic effects of reductions in plasma albumin concentration that occur early in the development of malnutrition should be substantial, but this is not the case. Fig. 1 illustrates the situation in children from Uganda and The Gambia. The curves fitted (cubic functions using log data) are not significantly different for the two groups of children but provide significantly better fits than either linear or quadratic plots and show that plasma colloid osmotic pressure is, on average, relatively stable in the higher albumin

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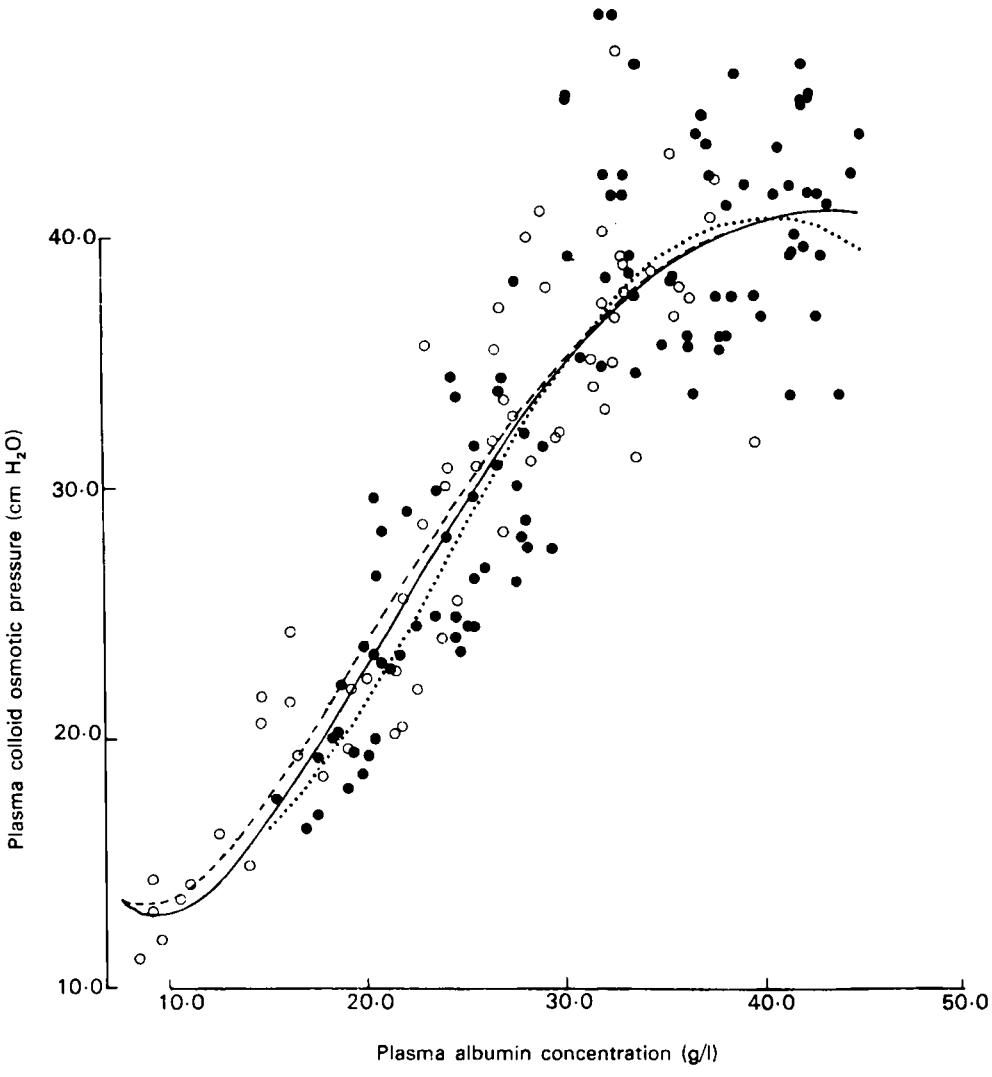

Fig. 1. Relationships between plasma albumin and colloid osmotic pressure in rural Gambian, (●.....); Ugandan, (○— - —); and all children (———).

concentration ranges. Therefore, in terms of changes in plasma colloid osmotic pressure and oedema pathogenesis little significance need to be attached to early changes in plasma albumin concentration.

At this point it is worthwhile recalling the suggestions of Bjørneboe (1946) and Rothschild *et al.* (1966) who postulated that rates of albumin synthesis are oncotically regulated. There is now experimental evidence to support this view. In perfused rat livers rates of albumin synthesis vary inversely with the colloid osmotic pressure of the perfusate (Ryoo & Tarver, 1968; Rothschild *et al.* 1969; Dich *et al.* 1973) and are depressed, in vivo, after infusions of dextran or

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hyperimmunization (Rothschild *et al.* 1961; Rothschild *et al.* 1962; Rothschild *et al.* 1965). It is reasonable to suggest, therefore, that some of the variations in albumin concentration in Gambian and Ugandan children are not due to the effect malnutrition has on rates of albumin synthesis, but, when plasma colloid osmotic pressure is normal, to the oncotic effects of variations in the concentration of other plasma proteins and the need to maintain plasma colloid osmotic pressure within a normal range.

Physiological significance of colloid osmotic pressure gradients at normal and low plasma protein concentrations

It has been shown that if assessments are to be made of the role plasma proteins play in oedema formation it will always be preferable to measure colloid osmotic pressure rather than to make judgments based on changes in protein concentration. Squire (1953) realized this and his studies on the significance of hypoalbuminaemia in the formation of oedema in the nephrotic syndrome are relevant to our present discussion. While the absolute level of plasma colloid osmotic pressure is important since this has to be related to the level of a pressure gradient across the capillaries at which there is no net movement of fluid through the capillary wall, the slope of the curve, when colloid osmotic pressure is plotted against protein concentration, is of greater significance. At normal plasma protein concentrations a 1% concentration change produces a 0·71 cm H_2O change in colloid osmotic pressure; in nephrotic serum, with a colloid osmotic pressure similar to that found in children with oedematous malnutrition, the gradient is much less steep (0·25 cm H_2O/1% concentration change) thus, taking the simplest possible view of capillary water filtration, the amount of haemoconcentration or loss of plasma ultrafiltrate that needs to occur to balance pressure against identical capillary pressure gradients has to be much greater in hypoproteinaemia than in normoproteinaemia.

Physiological significance of interstitial fluid colloid osmotic pressure and interstitial fluid hydrostatic pressure

Plasma colloid osmotic pressure is not the only force involved in determining rates of transcapillary water filtration; over-all fluid movements are determined by the total balance of hydrostatic and oncotic forces on both sides of the capillary. Starling's equation which is now usually written as

$$J = kf(Pc - \sigma\pi p - Pi + \sigma\pi i)$$

describes the forces involved.

Where: J, net capillary filtration rate; Pc, capillary hydrostatic pressure; Pi, interstitial fluid hydrostatic pressure; πp, plasma colloid osmotic pressure; πi, interstitial fluid colloid osmotic pressure; *kf*, capillary filtration coefficient; σ, reflection coefficient.

Under normal circumstances there is a small net fluid loss from the capillaries into interstitial fluid but the fluid returns to the circulation through the lymph vessels so that lymph flow rate is equivalent to the net rate of loss of fluid from the circulation and so long as this steady-state can be maintained, interstitial fluid

volume will remain constant. It is, therefore, important to realize that the relationship between the maximum carrying capacity of the lymphatics and the burden of filtered fluid that the lymphatic system is required to remove that will determine whether or not oedema appears.

Most workers now agree that interstitial fluid pressure is negative under normal conditions in most tissues (Guyton, 1963; Guyton *et al.* 1971; Scholander *et al.* 1968; Snashall *et al.* 1971; Fadnes, 1975) but Guyton (1972) has shown that when there is an increased load of filtered fluid into the interstitium, interstitial fluid pressure increases, without large changes in fluid volume, so that lymph flow rates increase; i.e. the compliance of the interstitial space is low. However, when interstitial fluid pressure approaches zero the compliance of the interstitial space increases enormously so that interstitial fluid volume can increase and lymph flow rates remain unchanged at maximum values.

Another theoretical consequence of increasing rates of fluid flow through the interstitial space is to lower the concentration of interstitial fluid protein. This will occur because the rate at which plasma proteins are transferred across the capillary wall is at most only partly dependent on rates of water filtration, therefore protein washed out of interstitial space by an increased rate of the bulk flow of fluid is not replaced as quickly as it is removed. Renkin's equation (Renkin, 1964) describes this phenomenon:

$$\frac{Ci}{Cp} = \frac{P}{P + V_L}$$

Where: Cp, solute concentration in plasma; Ci solute concentration in lymph or interstitial fluid; P, capillary membrane permeability to solute; V_L, lymph flow rate.

This equation assumes that protein escapes from the capillaries only by diffusion but comparable equations can be described in which some protein transport by bulk-flow across the capillary wall is allowed (Schultze & Heremans, 1966). Thus increasing rates of filtration and lymph flow will result in an altered set of osmotic forces across the capillary wall (assuming $\frac{Ci}{Cp} \simeq \frac{\pi i}{\pi p}$) that will tend to oppose further increase in rates of water filtration.

Given these considerations it becomes important that we should know not only how plasma colloid osmotic pressure changes in chronic malnutrition but also what the effects on interstitial fluid colloid osmotic pressure and interstitial fluid hydrostatic pressure are.

These factors have been investigated in our own recent studies (M. Fiorotto & W. A. Coward, unpublished results). Interstitial fluid is only usually obtainable in the pathological state when oedema formation has occurred but fluid can be collected from perforated capsules implanted sub-cutaneously for the measurement of interstitial fluid pressure using the method of Guyton (1963).

Changes in the absolute value of plasma oncotic pressure (πp) and interstitial fluid oncotic pressure (πi) in normal and hypoproteinaemic animals are shown in

Table 1. *Values (cm H_2O) for colloid osmotic pressures of plasma (πp) and interstitial fluid (πi), their ratio (πp:πi), interstitial fluid pressure (Pi) and the sum of forces opposing filtration (πp–πi+Pi) in rats fed on diet C (P:E 0·210) or diet VLP (P:E 0·005)*

(Values are means with their standard errors)

Time in experiment (weeks)	Diet	No. of Animals	πp Mean	πp SE	πi Mean	πi SE	Pi Mean	Pi SE	πp:πi Mean	πp:πi SE	πp–πi+Pi Mean	πp–πi+Pi SE
0	C	7	25·5	0·4	14·3	0·5	−1·3	0·2	1·8	0·1	10·1	0·5
2	C	7	27·0	0·5	13·8	0·6	−1·5	0·2	2·0	0·1	11·9	1·1
2	VLP	8	20·3	$0·6^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	7·0	$0·4^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	−2·6	$0·1^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	3·0	$0·2^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	10·7	0·7
5	C	6	27·1	0·8	13·6	0·4	−3·2	$0·3^{\bullet\bullet\bullet}$	2·0	0·1	10·2	1·1
5	VLP	8	19·2	$0·3^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	6·4	$0·7^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	−3·3	$0·4^{\bullet\bullet\bullet}$	3·2	$0·3^{\bullet\bullet\bullet}_{\dagger\dagger}$	9·5	0·7
9·5	VLP	6	18·1	$0·3^{\bullet\bullet\bullet}$	4·8	$0·1^{\bullet\bullet\bullet}$	−2·2	$0·1^{\bullet\bullet\bullet}$	3·8	$0·1^{\bullet\bullet\bullet}$	11·2	0·3
18–20	C	6	28·3	$1·0^{\bullet}$	13·9	0·8	−3·0	$0·5^{\bullet\bullet\bullet}$	2·1	$0·1^{\bullet}$	11·5	0·9
18–20	VLP	3‡	11·9	$0·5^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	1·3	$0·3^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	−0·1	$0·1^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	9·8	$1·8^{\bullet\bullet\bullet}_{\dagger\dagger\dagger}$	10·1	0·1

Values significantly different from those at week 0: $^{\bullet}P<0·05$; $^{\bullet\bullet}P<0·01$; $^{\bullet\bullet\bullet}P<0·001$.
Values for groups fed on diet VLP significantly different from corresponding groups fed on diet C;
† $P<0·05$; †† $P<0·01$; ††† $P<0·001$.
Student's *t* test was used in the analysis.
‡ denotes oedematous animals.

Table 1. Although πi was normally half the value of πp, πi was reduced by about the same absolute amount as πp in hypoproteinaemia so that the percentage change in πi was very much greater than that in πp. Initially Pi fell in both groups of animals but when the oedematous state was reached values were close to zero. The consequence of these changes was that the sum of forces opposing filtration (assuming $\sigma=1$) were not changed during the experiment although the ratio πp:πi changed considerably. Alterations in plasma and interstitial fluid volume only occurred when oedema appeared.

It is evident that the maintenance of normal pressure gradients across the capillaries in hypoproteinaemia is mainly the result of changes in πi that compensate for changes in πp. The physiological consequences of this adaptation are shown in Fig. 2. If it is accepted that a value for πp − πi needs to be established

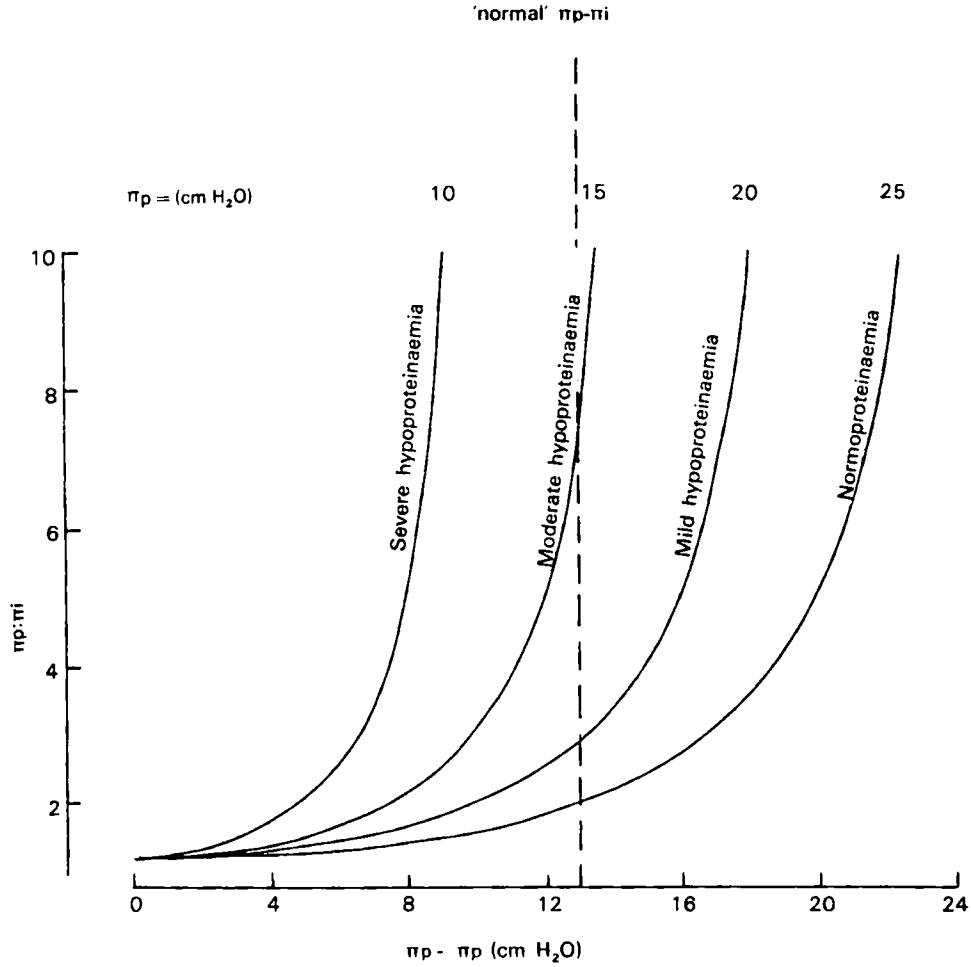

Fig. 2. Ratio, πp:πi, required to maintain normal values for πp−πi in rats.

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for the prevention of excessive water filtration it can be seen that this cannot be achieved, however small πi becomes, in severe hypoproteinaemia. In moderate hypoproteinaemia such a value could be reached but if capillary pressure were to be increased, or if the capillary filtration coefficient were to change in such a way that a larger difference was needed, once again no change in πi would be adequate to compensate.

This information provides an explanation for the prevention of oedema above a threshold value for πp but below which control over the distribution of extracellular fluid volume between the vascular and interstitial compartments is lost. Losses of fluid from plasma into the interstitial fluid compartment would trigger mechanisms to retain sodium and water but in the absence of alterations in πp the only effect of this adaptation would be to further expand interstitial fluid volume until, with increased tissue tension, increases in tissue pressure become sufficient to oppose filtration.

Taking this view of the significance of alterations in interstitial fluid oncotic pressure it can be seen that the well established redistribution of whole body albumin mass that occurs in malnutrition (see Coward & Sawyer, 1977) takes on particular physiological significance; this is not because extravascular protein buffers the plasma compartment but because loss of extravascular protein allows normal pressure gradients to be maintained.

Recalling the earlier description of the compliance of the interstitial space, the increases in interstitial fluid hydrostatic pressure that occurred in the protein-malnourished rats indicate increased rates of lymph flow, which, referring to Renkin's equation, would explain the change in interstitial fluid oncotic pressure, but there is an alternative view; that is that in malnutrition the capillary permeability to protein changes. Wraight (1974) showed that after plasmapheresis in rats, transcapillary escape rates for albumin are reduced and suggested that this is a factor allowing the maintenance of normal pressure gradients in hypoproteinaemia so that oedema formation can be prevented.

This latter explanation is somewhat cumbersome since it suggests that the capillary wall plays an active part in oedema prevention. It is, however, worth noting that in hypertensive subjects Parving *et al.* (1974) have demonstrated a significant positive correlation between fractional rates of albumin catabolism and transcapillary escape rates. Since it is generally accepted that rates of albumin catabolism are reduced in protein malnutrition it is possible that capillary permeability to albumin might also be reduced.

Changes in plasma protein concentration during loss of oedema

A frequent criticism expressed by those who do not accept the view that plasma protein concentration is significant in oedema formation in malnutrition is that in some instances, in individual children, oedema disappears without any changes in plasma albumin concentration. Reservations may immediately be expressed about these observations when plasma colloid osmotic pressures are not measured, however, if one examines the relationship between plasma colloid osmotic pressure

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and grades of oedema (Coward, 1975) it is clear that although the general trends are in the right direction, that is to say colloid osmotic pressure increases as oedema becomes less severe, there is considerable variation in values for colloid osmotic pressure in individual children with the same amount of oedema. Accepting a threshold concept for oedema formation leads us to the view that the extent of oedema will ultimately depend on the magnitude of sodium and water retention and sodium intake, furthermore a threshold implies that circumstances for oedema appearance or disappearance will exist over only a small range of values of plasma colloid osmotic pressure. There is a further complication: changes in plasma colloid osmotic pressure are the result of changes in both total active oncotic mass and plasma volume. As Reiff (1970) has pointed out increases in total active oncotic mass could produce changes both in concentration and volume. Increases in plasma volume during recovery from malnutrition are often observed and are illustrated by the data of Viart (1977). During the loss of oedema in thirteen children recovering from kwashiorkor the mean increment in plasma albumin concentration was 41% but at the same time total circulating albumin mass increased by 93%; examples from individual children are even more informative, in one case plasma albumin concentration increased from 12·0 to 14·4 g/l during loss of oedema but total circulating albumin mass increased from 3·5 to 5·6 g. It seems that measurement of plasma protein concentration during recovery can be somewhat misleading.

Summary and conclusions

It was not the purpose of this review to cover all the factors that might be involved in oedema formation in malnutrition but rather to indicate what significance changes in plasma protein concentration may have. It would be wrong to suggest that oedema formation can occur without sodium and water retention but it is evident that hypoproteinaemia produces circumstances in which sodium and water retention will cause severe oedema.

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